alleviate transcriptional defects caused by the inactive SWI/SNF components. Crystal structures indicate alterations in local structure and stability, but the influence of these mutations on nucleosome dynamics and packing is not well understood. Here we analyze 1,020 ns of all atom molecular dynamics multiple replica simulation data of five SIN mutant mononucleosomes (H3-E105K, H3-R116H, H3-T118I, H4-V43I and H4-R45H) and a wild type human mononucleosome.

Our simulations establish that SIN mutations influence the overall conformational state of nucleosomes, confer flexibility to the histone tails and alter the nucleosome core. Significant changes of N terminal tails of H3 and H2B as evidenced by RMS deviations are noted. The large fluctuations correlate with an increased mean radius of gyration in H3-R116H and H4-V43I. Hydrogen bond interaction profiles confirm changes in the nucleosome core packing. Analysis of the intra and extra base pair helical parameters indicate that SIN mutations induce significant differences in mean helical parameter values at SHLs ± 0.5, ± 3.5, ± 4.5 and ± 6.5, indicating that there exist multiple solutions for the path of the DNA superhelix at these locations. Each is an important site for association with SWI/SNF subunits. At SHLs (0, ± 2.0, ± 3.0) the path is clearly restricted. We have thus identified a multi-modal dynamic mechanism through which SIN mutants alter the behavior of the tails, as well as, the nucleosome core. Both affect the higher order structure of chromatin but through distinct mechanisms. Such mutations impact remodeling events during disease states and are being explored for functional roles in cancer.

1603-Pos Board B554

Quinone Binding in Bacterial Photosynthetic Reaction Center

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Quinones play a crucial role in transmembrane electron and proton transfer in proteins, thereby creating a gradient that is utilized for energy conversion. The medicinal properties of these molecules render them important for drug design. The quinone binding site varies considerably across different proteins and any strict binding motif is not defined yet. The bacterial photosynthetic reaction center (BRC) is one such protein with two quinone binding sites - QA and QB. Kinetic studies have shown differently substituted foreign quinones to be good binders at the QA site, however there are no protein structures available with the foreign quinones. The goal of this computational study is to derive a BRC-quinone interaction signature, with different quinones docked at the QA site. The derived signature could pave the way for future computer aided drug design, targeted at quinone binding proteins.

Sets of substituted foreign quinones were built and optimized in Gaussian09 and docked into the BRC QA site with AutoDock4.2. The protein-ligand vanderwaals overlap was calculated in Chimera. Analyses of the van der waals interaction of the complexes brought out a pattern of favorable interactions of the ligand with the protein, that directly correlate with high binding affinity. The benzoquinone strong binders showed favorable interaction with TrpM252, MetM256 and MetM262 of the BRC. The methyl and methoxy flanking a carbonyl formed a benzoquinone ligand-motif for strong binding. LeuM215, TrpM252, Met256, PheM258, MetM262, and IleM265 of the receptor favorably interacted with the strong naptho binders. Future work includes Molecular dynamics studies that will involve the FEP method on the docked complexes in NAMD2.9.

1604-Pos Board B555

Molecular Dynamic Simulation Studies on LolA and LolB Proteins in E. coli

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The Lol system in E.coli is involved in localization of lipoproteins and hence is essential for survival of the organism. In this system, LolA is a periplasmic chaperone that binds to outer-membrane specific lipoproteins and transports them from inner to outer membrane through another intermediary protein, LolB. A hydrophobic lipid-binding cavity constituted by α-helices is responsible for the transfer of lipoproteins from LolA to LolB. The current study aims to investigate conformational changes observed in both these proteins during this transfer using a detailed computational approach. Structural change observed in LolA during the transition from ''open to closed'' conformation forms the first step in this transfer process. In our Molecular Dynamic Simulation Studies, an open structure LolA(R43L) and an in-silico point mutated structure (MsL43R) were exposed to water for 50ns to simulate the periplasmic environment. Important residues involved in these structural changes and the corresponding forces (H-bonding and hydrophobic interactions) responsible for the stability of these conformational changes are also identified. Our analysis reveals that the structural flexibility of LolA is an important factor for its role as a periplasmic chaperone. This study also elucidates the functional role played by active residues during protein-protein interactions such as LolA-Pal and LolB-Pal. The acyl binding regions of the structures were identified and compared with experimental results obtained by Nakada et al., 2009. A novel structure based drug targeting has been attempted for inhibition of LolA-PAL and LolB-PAL interactions. Globomycin and related drug molecules were used as substrates for docking to the active sites of LolA and LolB which are identified by our protein-protein interaction studies.

1605-Pos Board B556

The Role of the Ion Dehydration Process in Low and High Conductance K Channels

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Potassium channels are known for exhibiting a wide conductance rate from 8.2 pS to 250 pS despite that selectivity filter is largely conserved. Some aspects about the relation between the charge distribution along to the pore and the conductance rate have been studied. In Shaker channel, a low conductance K-channel, one single point mutation of the P475D increases the 4-fold the maximal unitary conductance. At the same time, BK channels, a large conductance K-channel, has been demonstrated that a ring of negative charged residues in the intracellular entrance are key residues in the control of the maximal ion transport rate. Another main difference between low and high conductance K-channels is the size of the channel pore, BK has a much wider internal vestibule than Shaker. In order to understand at the molecular level the conduction process in both K^+ channel classes, we performed molecular dynamics simulations using an applied external electric field to compare the structural properties of BK and Shaker channels (+300 mV, +600 mV and +800mV). Different ranges of currents were observed in Shaker and BK under the influence of the external electric field. At all the voltages tested, BK present the largest rate of ion translocation. Interestingly, K^+ ions moving from the intracellular side up to the S4 site show a dehydration pattern, which is more efficient in BK channels. Other channel structural properties are discussed in the context of the dehydration process of the K ions in Shaker and BK.

Acknowledgements: CINV is a Millennium Institute. R.S thanks CONICYT doctoral fellowship and project FONDECYT 1110430 (RL), 1131003 (FGN), 1120819 (DN) and proyecto Anillo ACT1107 (FGN)

1606-Pos Board B557

Computational Design of Allosteric Inhibitors of AKT and SGK Kinases

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This research addresses computational design of small drug-like molecules that could potentially inhibit AKT and SGK kinases and thus stave off cancer advancement. AKT and SGK belong to the AGC group of protein kinases. They regulate important cell functions and their deregulation can lead to carcinogenesis. AKT and SGK are highly homologous, having similar activators and targets. Research showed that cancers with high SGK activity may develop resistance to AKT-specific inhibitors. In this work, we study putative dual AKT/SGK inhibitors that could hinder the development of the tumor resistance. Most kinase inhibitors target the kinase ATP-binding site. However, the high similarity in the ATP-binding site among kinases makes them challenging to target specifically. The specificity is essential, since drugs that indiscriminately bind several kinases may harm healthy tissue. Furthermore, mutations in the ATP-binding site can cause resistance to ATP-competitive kinase inhibitors. AKT and SGK have allosteric pockets, analogous to the PIF-pocket, which could be targeted. Molecules known to inhibit AKT were used as initial templates to design dual-specific inhibitors that targeted the allosteric binding sites of AKT and SGK. Physical and chemical properties of the sites were investigated and compared. The findings were used to design novel molecules that could potentially bind both AKT and SGK. Potential toxicities and drug-likeness of the molecules were evaluated. Molecules with no implied toxicities and optimal drug-like properties were used for docking studies. Binding energies of the stable complexes that these molecules formed with AKT and SGK were calculated. Possible utilization of the designed molecules against tumors with overexpressed AKT/SGK is discussed.